Labeling Guidance
April, 1995

DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE ORAL SOLUTION, USP

DESCRIPTION:

Each 5 mL, for oral administration, contains:
Diphenoxylate Hydrochloride....2.5 mg
(Warning-May be habit forming)
Atropine Sulfate.....0.025 mg

In addition, the following inactive ingredients are present...

[NOTE: We note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond accordingly by correctly noting the inactive ingredients present in this product.]

Diphenoxylate hydrochloride, an antidiarrheal, is ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate monohydrochloride and has the following structural formula:

Molecular formula $C_{30}H_{32}N_2O_2 \bullet HCL$ M.W.= 489.06

Atropine sulfate, an anticholinergic, is Benzeneacetic acid,-(hydroxymethyl)-8-methyl-8-azabicyclol[3.2.1] oct-3-yl ester, *endo*-±,sulfate(2:1)(salt), monohydrate and has the following structural formula:

Molecular formula $(C_{17}H_{23}NO_3)_2 \bullet H_2SO_4 \bullet H_2O$ M.W.= 694.85

A subtherapeutic amount of atropine sulfate is present to discourage deliberate overdosage.

CLINICAL PHARMACOLOGY

Diphenoxylate is rapidly and extensively metabolized in man by ester hydrolysis to diphenoxylic acid (difenoxine), which is biologically active and the major metabolite in the blood. After a 5 mg oral dose of carbon-14 labeled diphenoxylate hydrochloride in ethanolic solution was given to three healthy volunteers, an average of 14% of the drug plus its metabolites was excreted in the urine and 49% in the feces over a four-day period. Urinary excretion of the unmetabolized drug constituted less than 1% of the dose, and diphenoxylic acid plus its glucuronide conjugate constituted about 6% of the dose. In a sixteen-subject cross-over bioavailability study, a linear relationship in the dose range of 2.5 to 10 mg was found between the dose of diphenoxylate hydrochloride (given as Diphenoxylate HCl and Atropine Sulfate Oral Solution) and the peak plasma concentration, the area under the plasma concentration-time curve, and the amount of diphenoxylic acid excreted in the urine. In the same study the bioavailability of the tablet compared with an equal dose of the liquid was approximately 90%. The average peak plasma concentration of diphenoxylic acid following ingestion of four 2.5 mg tablets was 163 ng/mL at about 2 hours, and the elimination half-life of diphenoxylic acid was approximately 12 to 14 hours.

In dogs, diphenoxylate hydrochloride has a direct effect on circular smooth muscle of the bowel, that conceivably results in segmentation and prolongation of gastrointestinal transit time. The clinical antidiarrheal action of diphenoxylate hydrochloride may thus be a consequence of enhanced segmentation that allows increased contact of the intraluminal contents with the intestinal mucosa.

INDICATIONS AND USAGE

Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution is effective as adjunctive therapy in the management of diarrhea.

CONTRAINDICATIONS

Diphenoxylate HCl and Atropine Sulfate Oral Solution is contraindicated in patients with:

1. Known hypersensitivity to diphenoxylate or atropine.

2. Obstructive jaundice.

3. Diarrhea associated with pseudomembranous enterocolitis or enterotoxin-producing bacteria.

WARNINGS

THIS IS *NOT* AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. DIPHENOXYLATE HCl and ATROPINE SULFATE IS NOT RECOMMENDED FOR CHILDREN UNDER 2 YEARS OF AGE. OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH (SEE OVERDOSAGE). THEREFORE, KEEP THIS MEDICATION OUT OF THE REACH OF CHILDREN.

THE USE OF DIPHENOXYLATE HCl AND ATROPINE SULFATE SHOULD BE ACCOMPANIED BY APPROPRIATE FLUID AND ELECTROLYTE THERAPY, WHEN INDICATED. IF SEVERE DEHYDRATION OR ELECTROLYTE IMBALANCE IS PRESENT, THIS PRODUCT SHOULD BE WITHHELD UNTIL APPROPRIATE CORRECTIVE THERAPY HAS BEEN INITIATED. DRUG-INDUCED INHIBITION OF PERISTALSIS MAY RESULT IN FLUID RETENTION IN THE INTESTINE, WHICH MAY FURTHER AGGRAVATE DEHYDRATION AND ELECTROLYTE IMBALANCE.

DIPHENOXYLATE HCl AND ATROPINE SULFATE SHOULD BE USED WITH SPECIAL CAUTION IN YOUNG CHILDREN BECAUSE THIS AGE GROUP MAY BE PREDISPOSED TO DELAYED DIPHENOXYLATE TOXICITY AND BECAUSE OF THE GREATER VARIABILITY OF RESPONSE IN THIS AGE GROUP.

Antiperistaltic agents may prolong and/or worsen diarrhea associated with organisms that penetrate the intestinal mucosa (toxigenic *E. Coli, Salmonella, Shigella*), and pseudomembranous enterocolitis associated with broad-spectrum antibiotics. Antipersistaltic agents should not be used in these conditions.

In some patients with acute ulcerative colitis, agents that inhibit intestinal motility or prolong intestinal transit time have been reported to induce toxic megacolon. Consequently, patients with acute ulcerative colitis should be carefully observed and Diphenoxylate HCL and Atropine Sulfate therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop.

Since the chemical structure of diphenoxylate hydrochloride is similar to that of meperidine hydrochloride, the concurrent use of this product with monoamine oxidase (MAO) inhibitors may, in theory, precipitate hypertensive crisis.

This product should be used with extreme caution in patients with advanced hepatorenal disease and in all patients with abnormal liver function since hepatic coma may be precipitated.

Diphenoxylate hydrochloride may potentiate the action of barbiturates, tranquilizers, and alcohol. Therefore, the patient should be closely observed when any of these are used concomitantly.

PRECAUTIONS

General: Since a subtherapeutic dose of atropine has been added to the diphenoxylate hydrochloride, consideration should be given to the precautions relating to the use of atropine. In children, Diphenoxylate HCl and Atropine Sulfate should be used with caution since signs of atropinism may occur even with recommended doses, particularly in patients with Down's syndrome.

Information for Patients: INFORM THE PATIENT (PARENT OR GUARDIAN) NOT TO EXCEED THE RECOMMENDED DOSAGE AND TO KEEP THIS PRODUCT OUT OF THE REACH OF CHILDREN AND IN A CHILD-RESISTANT CONTAINER. INFORM THE PATIENT OF THE CONSEQUENCES OF OVERDOSAGE, INCLUDING SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH. Diphenoxylate HCl and Atropine Sulfate may produce drowsiness or dizziness. The patient should be cautioned regarding activities requiring mental alertness, such as driving or operating dangerous machinery. Potentiation of the action of alcohol, barbiturates, and tranquilizers with concomitant use of this product should be explained to the patient. The physician should also provide the patient with other information in this labeling, as appropriate.

Drug Interactions: Known drug interactions include barbiturates, tranquilizers, and alcohol. Diphenoxylate HCl and Atropine Sulfate may interact with MAO inhibitors (see WARNINGS).

In studies with male rats, diphenoxylate hydrochloride was found to inhibit the hepatic microsomal enzyme system at a dose of 2 mg/kg/day. Therefore, diphenoxylate has the potential to prolong the biological half-lives of drugs for which the rate of elimination is dependent on the microsomal drug metabolizing enzyme system.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term study in animals has been performed to evaluate

carcinogenic potential. Diphenoxylate hydrochloride was administered to male and female rats in their diets to provide dose levels of 4 and 20 mg/kg/day throughout a three-litter reproduction study. At 50 times the human dose (20 mg/kg/day), female weight gain was reduced and there was a marked effect on fertility as only 4 of 27 females became pregnant in three test breedings. The relevance of this finding to usage of Diphenoxylate HCl and Atropine Sulfate in humans is unknown.

Pregnancy: Pregnancy Category C. Diphenoxylate hydrochloride has been shown to have an effect on fertility in rats when given in doses 50 times the human dose (see above discussion). Other findings in this study include a decrease in maternal weight gain of 30% at 20 mg/kg/day and of 10% at 4 mg/kg/day. At 10 times the human dose (4 mg/kg/day), average litter size was slightly reduced.

Teratology studies were conducted in rats, rabbits, and mice with diphenoxylate hydrochloride at oral doses of 0.4 to 20 mg/kg/day. Due to experimental design and small numbers of litters, embryotoxic, fetotoxic, or teratogenic effects cannot be adequately assessed. However, examination of the available fetuses did not reveal any indication of teratogenicity.

There are no adequate and well-controlled studies in pregnant women. This product should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers: Caution should be exercised when this product is administered to a nursing woman, since the physicochemical characteristics of the major metabolite, diphenoxylic acid, are such that it may be excreted in breast milk and since it is known that atropine is excreted in breast milk.

Pediatric use: Diphenoxylate HCl and Atropine Sulfate may be used as an adjunct to the treatment of diarrhea but should be accompanied by appropriate fluid and electrolyte therapy, if needed. DIPHENOXYLATE HCl AND ATROPINE SULFATE IS NOT RECOMMENDED FOR PEDIATRIC PATIENTS UNDER 2 YEARS OF AGE. Diphenoxylate HCl and Atropine Sulfate should be used with special caution in young children because of the greater variability of response in this age group. See WARNINGS and DOSAGE AND ADMINISTRATION. In case of accidental ingestion by children, see OVERDOSAGE for recommended treatment.

ADVERSE REACTIONS

At *therapeutic* doses, the following have been reported; they are listed in decreasing order of severity, but not of frequency:

Nervous system: Numbness of extremities, euphoria, depression, malaise/lethargy, confusion, sedation/drowsiness, dizziness, restlessness, headache.

Allergic: anaphylaxis, angioneurotic edema, urticaria, swelling of the gums, pruritus.

Gastrointestinal system : toxic megacolon, paralytic ileus, pancreatitis, vomiting, nausea, anorexia, abdominal discomfort.

The following atropine sulfate effects are listed in decreasing order of severity, but not of frequency: hyperthermia, tachycardia, urinary retention, flushing, dryness of the skin and mucous membranes. These effects may occur, especially in children.

THIS MEDICATION SHOULD BE KEPT IN A CHILD-RESISTANT CONTAINER AND OUT OF THE REACH OF CHILDREN SINCE AN OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH.

DRUG ABUSE AND DEPENDENCE

Controlled substance: Diphenoxylate HCl and Atropine Sulfate Tablets/Oral Solution are classified as a Schedule V controlled substance by federal regulation. Diphenoxylate Hydrochloride is chemically related to the narcotic analgesic meperidine.

Drug Abuse and Dependence: In doses used for the treatment of diarrhea, whether acute or chronic, diphenoxylate has not produced addiction.

Diphenoxylate hydrochloride is devoid of morphine-like subjective effects at therapeutic doses. At high doses it exhibits codeine-like subjective effects. The dose which produces antidiarrheal action is widely separated from the dose which causes central nervous system effects. The insolubility of diphenoxylate hydrochloride in commonly available aqueous media precludes intravenous self-administration. A dose of 100 to

300 mg/day, which is equivalent to 40 to 120 tablets, administered to humans for 40 to 70 days, produced opiate withdrawal symptoms. Since addiction to diphenoxylate hydrochloride is possible at high doses, the recommended dosage should not be exceeded.

OVERDOSAGE

RECOMMENDED DOSAGE SCHEDULES SHOULD BE STRICTLY FOLLOWED. THIS MEDICATION SHOULD BE KEPT IN A CHILD-RESISTANT CONTAINER AND OUT OF THE REACH OF CHILDREN, SINCE AN OVERDOSAGE MAY RESULT IN SEVERE, EVEN FATAL, RESPIRATORY DEPRESSION.

Diagnosis: Initial signs of overdosage may include dryness of the skin and mucous membranes, mydriasis, restlessness, flushing, hyperthermia, and tachycardia followed by lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, and respiratory depression. Respiratory depression may be evidenced as late as 30 hours after ingestion and may recur in spite of an initial response to narcotic antagonists. TREAT ALL POSSIBLE DIPHENOXYLATE HCl AND ATROPINE SULFATE OVERDOSAGES AS SERIOUS AND MAINTAIN MEDICAL OBSERVATION FOR AT LEAST 48 HOURS, PREFERABLY UNDER CONTINUOUS HOSPITAL CARE.

Treatment: In the event of overdosage, induction of vomiting, gastric lavage, establishment of a patent airway, and possibly mechanically assisted respiration are advised. *In vitro* and animal studies indicate that activated charcoal may significantly decrease the bioavailability of diphenoxylate. In non-comatose patients, a slurry of 100 g of activated charcoal can be administered immediately after the induction of vomiting or gastric lavage.

A pure narcotic antagonist (e.g., naloxone) should be used in the treatment of respiratory depression caused by Diphenoxylate HCl and Atropine Sulfate. When a narcotic antagonist is administered intravenously, the onset of action is generally apparent within two minutes. It may also be administered subcutaneously or intramuscularly, providing a slightly less rapid onset of action but a more prolonged effect.

To counteract respiratory depression caused by Diphenoxylate/Atropine overdosage, the following dosage schedule for the narcotic antagonist naloxone hydrochloride should be followed:

Adult dosage: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride has been administered, the diagnosis of narcotic-induced or partial narcotic-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Children: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone hydrochloride may be administered I.M. or S.C. in divided doses. If necessary, naloxone hydrochloride can be diluted with sterile water for injection.

Following initial improvement of respiratory function, repeated doses of naloxone hydrochloride may be required to counteract recurrent respiratory depression. Supplemental intramuscular doses of naloxone hydrochloride may be utilized to produce a longer-lasting effect.

Since the duration of action of diphenoxylate hydrochloride, is longer than that of naloxone hydrochloride, improvement of respiration following administration may be followed by recurrent respiratory depression. Consequently, continuous observation is necessary until the effect of diphenoxylate hydrochloride on respiration has passed. This effect may persist for many hours. The period of observation should extend over at least 48 hours, preferably under continuous hospital care. Although signs of overdosage and respiratory depression may not be evident soon after ingestion of diphenoxylate hydrochloride, respiratory depression may occur from 12 to 30 hours later.

DOSAGE AND ADMINISTRATION

DO NOT EXCEED RECOMMENDED DOSAGE.

Adults: The recommended initial dosage is 10 mL of oral solution (two regular teaspoonfuls) four times daily (20 mg per day). Most patients will require this dosage until initial control has been achieved, after which the dosage may be reduced to meet

individual requirements. Control may often be maintained with as little as 5 mg (10 mL of liquid) daily.

Clinical improvement of acute diarrhea is usually observed within 48 hours. If clinical improvement of chronic diarrhea after treatment with a maximum daily dose of 20 mg of diphenoxylate hydrochloride is not observed within 10 days, symptoms are unlikely to be controlled by further administration.

Children: Diphenoxylate HCl and Atropine Sulfate is not recommended in children under 2 years of age and should be used with special caution in young children (see WARNINGS and PRECAUTIONS). The nutritional status and degree of dehydration must be considered. In children under 13 years of age, use oral solution. Do not use tablets for this age group.

Only the plastic dropper should be used when measuring the oral solution for administration to children.

Dosage schedule for children. The recommended initial total daily dosage of Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution for children is 0.3 to 0.4 mg/kg administered in four divided doses. The following table provides an *approximate* initial daily dosage recommendation for children.

Age (Years)	Approximate Weight (kg)	Weight (lb)	Dosage in mL (four times daily)
2	11-14	24-31	1.5-3
3	12-16	26-35	2-3
4	14-20	31-44	2-4
5	16-23	35-51	2.5-4.5
6-8	17-32	38-71	2.5-5
9-12	23-55	51-121	3.5-5

These pediatric schedules are the best approximation of an average dose recommendation which may be adjusted downward according to the overall nutritional status and degree of dehydration encountered in the sick child. Reduction of dosage may be made as soon as initial control of symptoms has been achieved. Maintenance dosage may be as low as one-fourth of the initial daily dosage. If no response occurs within 48 hours,

Diphenoxylate HCl and Atropine Sulfate is unlikely to be effective.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

HOW SUPPLIED

-established name
-strength of the dosage form
-packaging
-color, flavor,
-NDC number
-Special handling and storage conditions

-Date of Revision
-Manufactured By statement